Strategies to improve the outcome of biliary atresia

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General discussion and future perspectives

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Chapter 9

In the past decades, biliary atresia (BA) has evolved in the past decades from a uniformly lethal disease to a disease with two potentially life-saving treatment options. Nevertheless, BA is still a serious disease with substantial mortality (~10-20% at the age of 4) and morbidity.[32,147,151,203] The relative rarity renders the disease difficult to study.[60] Even observational studies and trials executed in large countries may not have sufficient power to detect small but potentially clinically relevant differences.[30] To obtain a reasonable sample-size, multi-center research is necessary.

In the Netherlands, we have established the Netherlands Study group on Biliary Atresia Registry (NeSBAR). The nationwide, prospective NeSBAR registry contains the relevant medical and surgical information of all diagnosed BA patients since 1987, including longitudinal follow-up. The national database not only allows us to monitor the quality of the Dutch BA care, but is also of potential international importance as it may provide clues for general improvement of BA treatment. A separate cohort of patients born between 1977 and 1986 (who were studied in the eighties)[68] could be traced back offering a unique study population. In this way, we could analyze the long-term outcome not only in terms of survival rates, but also examine the current clinical and psychological condition.

This thesis aimed to define the outcome of BA in the Netherlands and to compare it to available international data, and to identify (modifiable) prognostic factors. Together, this information is thought to help defining strategies to further improve the outcome of BA, both in the Netherlands and internationally.

Treatment of biliary atresia

The state of the art regarding clinical BA management is outlined in **Chapter 1**. The development of the portoenterostomy technique by Morio Kasai in 1959 was the first major breakthrough in the treatment of BA.[82] During the Kasai procedure, the obliterated bile ducts are excised, and a Roux-en-Y bowel loop is anastomosed to the porta hepatis of the liver. Now, it has become clear that patients may retain sufficient liver function for decades after the procedure.[103] Yet, a significant fraction of the patients experiences ongoing cholestasis and development of chronic end-stage liver disease, either rapidly or over the course of many years. The development and availability of liver transplantation (OLT) for children constituted another breakthrough. It is now generally accepted that the two treatment options, Kasai surgery and OLT, should be applied sequentially, as the chances of a long-term transplant-free survival cannot be predicted prior to the Kasai procedure.[60] In this way donor organs are spared. Furthermore, OLT still poses more risk when the procedure is performed in very young children.[38,47] Post-OLT survival rates are around 80% at ten years nowadays.[47] Nevertheless, living with a transplanted organ means longstanding use of immunosuppressants and carries its own morbidities. Improvement of the transplant-free survival is therefore of the utmost importance and has therefore been the focus of most research efforts.

OUTCOMES IN THE NETHERLANDS AND LESSONS TO BE LEARNED

BA in infancy and early childhood

OLT-candidates need early referral

As stated above, OLT is usually a lifesaving treatment option after development of end-stage liver disease despite Kasai surgery in BA patients. The timing of OLT , however is critical because of

the mortality of end-stage liver disease itself. In **Chapter 2** we have investigated the prevalence and causes of pre-transplant mortality in order to assess whether OLT indeed could have been a lifesaving treatment in those children who died without undergoing OLT. Although pre-transplant mortality had decreased in the Netherlands in two decades, it was still substantially higher than in other Western countries. The major cause of death was sepsis, followed by end-stage liver disease and thus, causes that could be envisioned to be, at least partly, preventable by timely OLT. When assessing the disease stage in which patients were referred for OLT, we found that patients with pre-transplant mortality were referred in a relatively late stage of disease as expressed by the pediatric end-stage liver disease score. Based on these findings, we concluded that measures should be (and are currently) taken to assure timely referral of potential OLT candidates. These findings might apply in other countries as well.

Current vitamin K prophylaxis regimen is not adequate in BA patients fed hydrolyzed formula
In a previous study using NeSBAR data, it was already shown that breastfed cholestatic infants are at a high risk for bleeding due to vitamin K deficiency, including intracranial hemorrhage in 43% of the studied patients. This was shown to be related to the relatively low dosage of vitamin K prophylaxis which was recommended by the at that time current national protocol.[187] Based on this analysis of the NeSBAR data in relation to available international results, the guideline of vitamin K prophylaxis for breast-fed infants has recently been adapted.[144] In **chapter 3**, we studied whether the a higher risk of vitamin K deficiency bleeding applied for cholestatic infants (BA patients, and patients with α-1 anti-trypsin deficiency) fed with hydrolyzed formula, a type of feeding which is increasingly used. These infants had a higher risk (risk ratio 25.0 [6.4–97.2], $p<0.001$) for vitamin K deficiency bleeding as well. The vitamin K content of hydrolyzed formula appeared to be similar to regular formula. Therefore, we could not find a proper explanation for the increased incidence of vitamin-K dependent bleeding. Although cholestatic diseases in infancy are rare, inadequate vitamin K dosage may have detrimental consequences in affected infants. Based on these two studies, the recommended dosage of vitamin will be adapted in the national protocol. Furthermore, the results of these studies should prompt other countries to revise their protocols, especially when breastfeeding or the use of hydrolyzed formula is substantial. Furthermore, manufacturers of infant formula should pay attention to the bioavailability of essential components in the distinct types of formula.

BA patients benefit from early surgery
In the past two decades, 214 patients underwent Kasai portoenterostomy in The Netherlands. Their outcomes are analyzed in **chapter 4**. The clearance of jaundice (bilirubin levels dropping below 17 μmol/L within 6 months post-surgery) rate and the transplant-free survival remained constant in the past two decades. However, this also means that the prognosis has not improved despite the progress in medicine in general. The results were similar to those in other western countries, despite a low case load of the treatment centers. Therefore, our transplant-free survival data do not provide direct arguments for the centralization of surgical treatment of BA.[32] Intuitively, a case-load ranging from one patient every two years to two patients annually does not give any surgeon the possibility to become experienced. Centralization may improve the outcome further and may also help to overcome the problems delineated in **Chapter 2**. Centralization post-Kasai FU Although the OLT rate improved during the past decades, the overall survival is still somewhat lower compared to other countries, underlining the findings of **Chapter 2**. We identified a younger age at Kasai surge-

ry, clearance of jaundice and use of postoperative antibiotic prophylaxis as independent factors positively associated with transplant-free survival. In addition, postoperative ursodeoxycholic acid (UDCA) use tended to be associated with both clearance of jaundice and transplant-free survival. Based on these results, we argued that more effort should be put forward to promote early referral of jaundiced infants and of infants with acholic stools, a major symptom of some forms of neonatal cholestatic disease, including BA.

It is difficult to distinguish among the many physiologically jaundiced infants the few patients with underlying disorders. A screening method adequately distinguishing cholestatic infants from infants with physiological jaundice is not available. However, if the child remains jaundiced at the age of 21 days, a measurement of the conjugated bilirubin fraction is warranted. Studies from Thailand have proven that an infant stool color card is helpful for parents and primary caregivers in distinguishing pathologic stool colors from the palette of infant stool colors, and improves the survival of BA patients.[71] During the period studies had been performed, our advice towards measurement of conjugated bilirubin has now been successfully implemented in the Dutch guideline concerning the treatment of jaundiced infants (guideline website: www.babyzietgeel.nl).[125] It seems reasonable to introduce (an analogue of) the infant stool color card in the Netherlands based on data from Taiwan.[98] It is a very cheap, non-invasive and effective method to detect cholestatic infants, which has been shown to increase 5-year transplant-free survival by 37%, and 5-year overall survival by 33% in the Taiwanese situation. It may function adequately in the highly organized Dutch infant health care system.

Post-Kasai BA patients may benefit from antibiotic and ursodeoxycholic acid administration

UDCA is a relatively hydrophilic bile acid with choleretic properties. Besides, some evidence suggests that it represses T-cell mediated hepatocellular damage and that it inhibits apoptosis.[93] It has been shown to increase the survival of primary biliary cirrhosis patients.[100] Only few studies examined the effects of UDCA in BA, with a study design not allowing for definite conclusions.[204] Nevertheless, it is prescribed on an appreciable scale to BA patients.

Antibiotics are frequently prescribed post-Kasai surgery, in order to decrease the risk of cholangitis, and thereby of progression of liver damage. However, the effects of antibiotics on outcome parameters have barely been studied.[17]

In our retrospective analysis (**chapter 4**), the use of postoperative antibiotic prophylaxis appeared to be independently associated with transplant-free survival. Postoperative UDCA use tended to be associated with both clearance of jaundice and transplant-free survival. These observational data do not allow for conclusions on whether these medicaments are beneficial in BA. First, the patients receiving UDCA were not randomized and thus not evenly distributed over the treatment centers. Second, non-blinding of physicians towards UDCA prescription might have influenced treatment decisions, and the study was not placebo-controlled. However, the data suggest a potentially beneficial effect, which deserves to be studied in an appropriate study design. Ideally, this would be a randomized controlled trial. As discussed before, however, it may be rather difficult to collect a sample size large enough to demonstrate clinical relevant effects. Therefore, it should be encouraged that such a study is undertaken on an international level.

BA in early adulthood

Most reports deal with the outcomes of BA on the relative short term (one to five years post-

surgery). As Kasai portoenterostomy became available as a potential curative treatment of BA in most western countries in the seventies, few cohort studies have investigated the outcome beyond twenty years. In the second part of the thesis, we set out to study the long-term outcome of BA patients surviving into adulthood in more detail in **chapter 5**, **6**, and **7**.

Clinical condition of adult transplant-free BA patients

First, we analyzed the survival rate and clinical condition of BA patients at 20 years post-Kasai (**chapter 5**). About one third of all BA patients survive without transplantation beyond the age of 20. Five percent of all BA patients does so with normal serum liver biochemistry parameters, and absent signs of liver cirrhosis or portal hypertension on ultrasound. It is currently unknown whether these patients are still at risk for disease progression, or whether they can be considered 'cured'. It is expected that a considerable fraction of the long-term transplant-free survivors will require OLT sooner or later. We found a trend towards a higher transplant-free survival in patients with the BA subtypes I and II, compared to those with subtype III. We could not distinguish an effect of age at surgery on 20-year transplant-free survival. Our study (104 BA patients) is probably underpowered to detect such an effect a large study from France (695 BA patients) detected a positive effect of younger age at surgery up to 15 years post-Kasai.[152] Interestingly, two patients from our study with very late surgery (> 90 days of age) survived without OLT into adulthood. Thus, even in late presenting patients it is worthwhile to perform portoenterostomy as a primary treatment, in agreement with current recommendations.[60] We did not identify comorbidities plausibly related to BA in the studied patient group, such as hepatic malignancies or gallstones. These data show that long-term transplant-free survival is possible in a substantial number of patients. However, in this study we could not find modifiable factors associated with survival.

Quality of life and course of life of adult BA patients

A number of studies have been addressing the health-related quality of life (HRQOL) in adult patients with chronic cholestatic liver disease, and HRQOL has been extensively studied in patients after OLT. However, BA is a rare disease, and there are few adult BA patients at the moment. Thus, BA patients are by definition underrepresented in those studies. As long-term survival (with or without OLT) is now achieved in up to 80% of the patients, the HRQOL of those patients could become an important aspect of disease management. The HRQOL of a group of 25 transplant-free and 15 transplanted young adult BA survivors is detailed in **chapter 6**. Overall, BA patients have a HRQOL (measured by the RAND-36 questionnaire) comparable to an age-matched reference group. Transplant-free female BA patients had a lowered general health perception, compared to transplant-free males and the reference group. There was also a tendency towards lowered physical role functioning in the transplant-free BA patients, with an effect size suggesting clinical relevance. HRQOL domain scores were not correlated to biochemical parameters of liver disease, but were correlated to liver disease symptom scores. Therefore, we concluded that liver disease symptom scores may be an important tool in the follow-up of patients with chronic liver disease to select those patients at risk for HRQOL problems who might need specialized attention. Transplant-free female BA patients and those with liver disease associated symptoms seem to be the patient groups most at risk for HRQOL problems.

BA is the most frequently occurring liver disease with an onset very early in life. Liver disease with associated symptoms such as longstanding high bilirubin levels may cause neuronal

damage, whereas malnutrition and ascites may hamper physical development.[19,153,213] Therefore, we measured the course of life of the same group of transplant-free and non-transplanted BA patients (**chapter 7**). In general, the course of life of BA patients was not delayed compared to age-matched peers. In this way BA patients seem to fare better than patients confronted with other serious conditions in childhood, such as childhood cancer and anorectal malformations.[165,166] Transplanted BA patients showed decreased risk behavior (smoking, gambling, alcohol use) which may be associated with the lifestyle recommendations they receive from their physicians. Transplant-free patients reported an alcohol consumption similar to age-matched peers, which might indicate that they do not adhere to their physicians' advice. This may be seen as compensatory risk behavior. Alcohol use should therefore be more actively discouraged in transplant-free patients. In general, it seems unnecessary to stimulate milestone achievement in BA patients, but analysis of the course of life in other BA cohorts is warranted.

Overall, the results concerning HRQOL and course of life in young adult BA patients were rather reassuring, in that BA patients (and their families) seem to be able to cope well with the sequelae of such a serious disease. It needs to be emphasized that the patient group studied for HRQOL and course of life is already a sub-selection of all BA patients. The sample size is small, what should be taken into account in their interpretation: the results are merely descriptive and studies in larger patient populations are certainly helpful for more detailed insights in this important area.